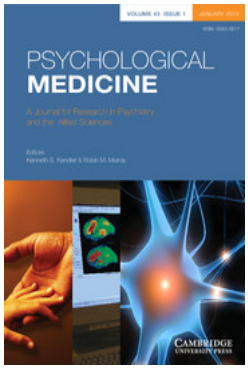

Gender difference in age at onset of schizophrenia: a meta-analysis

S. V. Eranti, J. H. MacCabe, H. Bundy and R. M. Murray

Psychological Medicine / Volume 43 / Issue 01 / January 2013, pp 155 - 167
DOI: 10.1017/S003329171200089X, Published online: 08 May 2012

Psychological Medicine (2013), **43**, 155–167. © Cambridge University Press 2012
doi:10.1017/S003329171200089X

ORIGINAL ARTICLE

Gender difference in age at onset of schizophrenia: a meta-analysis

S. V. Eranti[1]*†, J. H. MacCabe[2]†, H. Bundy[2] and R. M. Murray[3]

[1] *Newham Early Intervention Service, East London Foundation Trust, Stratford Office Village, London, UK*
[2] *Department of Psychosis Studies, Institute of Psychiatry, King's College London, de Crespigny Park, London, UK*
[3] *Institute of Psychiatry, King's College London, de Crespigny Park, London, UK*

Background. Most studies reporting the gender difference in age at onset of schizophrenia show an earlier onset in males, but vary considerably in their estimates of the difference. This may be due to variations in study design, setting and diagnostic criteria. In particular, several studies conducted in developing countries have found no difference or a reversed effect whereby females have an earlier onset. The aim of the study was to investigate gender differences in age of onset, and the impact of study design and setting on estimates thereof.

Method. Study methods were a systematic literature search, meta-analysis and meta-regression.

Results. A total of 46 studies with 29218 males and 19402 females fulfilled the inclusion criteria and were entered into a meta-analysis. A random-effects model gave a pooled estimate of the gender difference of 1.07 years (95% confidence interval 0.21–1.93) for age at first admission of schizophrenia, with males having earlier onset. The gender difference in age at onset was not significantly different between developed and developing countries. Studies using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria showed a significantly greater gender difference in age at onset than studies using International Classification of Diseases (ICD) criteria, the latter showing no difference.

Conclusions. The gender difference in age of onset in schizophrenia is smaller than previously thought, and appears absent in studies using ICD. There is no evidence that the gender difference differs between developed and developing countries.

Received 20 June 2011; Revised 21 March 2012; Accepted 26 March 2012; First published online 8 May 2012

Key words: Age at onset, gender difference, schizophrenia.

Introduction

Emil Kraepelin (1909–1915) was the first of many researchers to suggest that men develop schizophrenia at a younger age than women. Subsequent studies addressing this gender difference in age at onset have reported findings which vary considerably; in some studies the difference is as great as 5 years (Gureje & Bamidele, 1998), and in others it is absent (Murthy *et al*. 1998; Gangadhar *et al*. 2002). Thus, in a review of 53 studies, Angermeyer & Kuhn (1988) reported that the majority of studies found an earlier onset in men, but in five studies, especially those from developing countries, there was no difference between the genders. More recently, three studies in India produced anomalous results. Subbakrishna *et al*. (2001) and Murthy *et al*. (1998) failed to find any gender difference while Gangadhar *et al*. (2002) found an earlier onset in females. These findings have led to speculation that the gender effect is absent or reversed in developing countries (Gangadhar *et al*. 2002).

The variations may reflect the wide variety of definitions of age at onset. Some studies have used the first admission, some the first consultation, while others have taken the first symptom or first positive symptom. If males and females differ in their duration of untreated psychosis, or present to services at different stages of their illness, then different definitions of onset should give rise to variations in the gender difference.

A further issue is that diagnostic criteria for schizophrenia have different thresholds for length of illness. For example, the Diagnostic and Statistical Manual of Mental Disorders (DSM), Third Edition (DSM-III), Third Edition Revised (DSM-III-R) and Fourth Edition (DSM-IV) have a 6-month duration criterion while the International Classification of

* Address for correspondence: S. V. Eranti, Newham Early Intervention Service, East London Foundation Trust, Unit 9, Stratford Office Village, 4 Romford Road, London E15 4EA, UK.
(Email: savitha.eranti@kcl.ac.uk)
† These authors contributed equally to this work.

Diseases (ICD), Tenth Revision (ICD-10) requires only 1-month duration. Thus, briefer forms of psychosis are excluded by the DSM criteria for schizophrenia, but classified as schizophrenia in the ICD. This may be of relevance to the gender difference reported by different studies, as age at onset may vary with the severity and duration of psychosis (Castle *et al*. 1998).

No recent review has systematically reviewed the published studies on gender differences in age at onset in schizophrenia, and attempted to take into account variations in the design, methodology, and the sample selected. The present meta-analysis systematically reviews the studies published between 1987 and 2009, to obtain pooled estimates of gender difference based on these studies, and to ascertain factors that may influence it.

Method

Data sources

Ovid Medline and Web of Science databases were searched between 1987 and 2009 with the keywords 'age at onset and gender (or sex) and schizophrenia'. In addition, references were cross-checked from recent review articles related to the subject. Where relevant data were not available in the publication, the authors were contacted and the information requested.

Study selection

Only those articles or reports fulfilling the following criteria were included:

(1) Mean age at onset for schizophrenia (alone or with other psychosis) and standard deviation (S.D.) reported separately in males and females.
(2) Studies using ICD (version 9 or later) or DSM (version III or later).
(3) Studies published in English, in a peer-reviewed, indexed scientific journal.
(4) Age at onset defined as either age at first symptom, age at first positive symptom, age at first consultation or treatment, or age at first admission.
(5) Study not limited to extreme age groups such as under 18 years or over 65 years.

Exclusion criteria were as follows:

(1) Part of or the entire sample overlapped with a different publication that was already included. In such instances, the most inclusive study was used, and where this was not clear, the authors were contacted for clarification.
(2) The study was limited to childhood- and adolescent-onset psychosis or to cases with late onset ($\geqslant$45 years).

Data extraction

A total of 553 studies were identified and their abstracts screened. Where the abstract suggested that the study might contain relevant data, the paper was scrutinized. So, 46 studies were found to meet our criteria for inclusion.

Table A1 (see Appendix) shows summary data for the included studies. Where studies reported age at onset in more than one sample, each estimate was entered separately. For example, Stöber *et al*. (1998) reported separate data for periodic and systemic catatonia. These data were entered as separate estimates, namely Stöber a 1998 and Stöber b 1998.

Publication bias

Possible publication bias was investigated informally by means of a funnel plot (Everitt, 2003).

Meta-analysis procedure

Initial inspection of the studies revealed that the absolute age of onset varied considerably between studies, depending on the setting and inclusion criteria of the studies. However, the difference in age of onset between men and women was much more homogeneous. Therefore, the metric that we used in all our analyses was the age of onset in males minus the age at onset in females. Thus, negative numbers indicated an earlier onset in males. All analyses were conducted in Stata Version 10 for Macintosh (StataCorp LP, USA), using the METAN (Bradburn *et al*. 1988) and METAREG (Harbord & Higgins, 2008) procedures. The data from the separate studies showed heterogeneity in the estimated age at onset difference for men and women (heterogeneity among all studies: $\chi^2 = 313.53$, degrees of freedom = 50, $p < 0.001$). Furthermore, the studies were derived from a wide range of populations, using different definitions of age of onset and schizophrenia. Consequently a random-effects model was used to obtain a combined estimate and confidence interval (CI) of the gender difference in age at onset.

We conducted separate meta-analyses to obtain pooled estimates of gender difference in age at onset for studies using the following definitions of age at onset: (1) age at first symptom; (2) age at first positive symptom; (3) age at first consultation; and (4) age at first admission.

We also combined studies with the above definitions of age at onset for schizophrenia to obtain a pooled estimate of the gender difference. We then performed a further meta-analysis, where we relaxed the diagnostic criteria to include schizo-affective disorder and other non-affective psychoses. For this

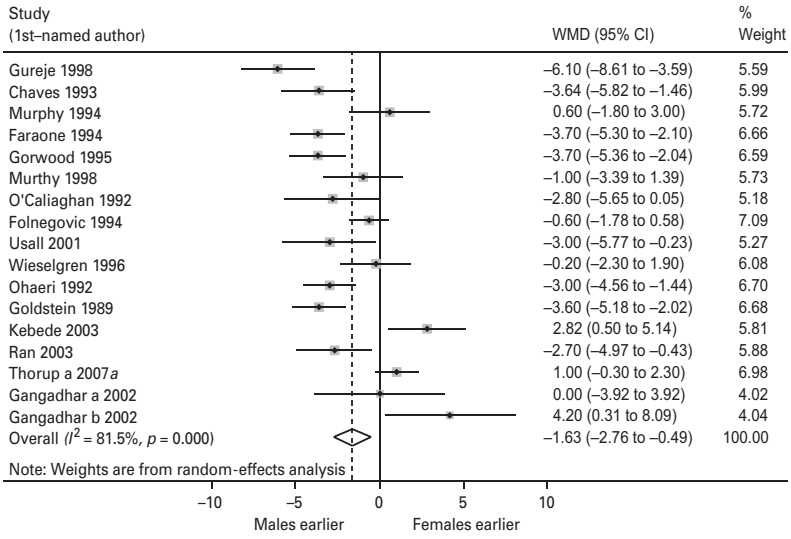

Fig. 1. Forest plot for gender difference in age (years) at first symptom of schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.

analysis, we took age at first admission as the definition of age at onset, since this was the most frequently reported definition.

Meta-regression

Meta-regression was used to assess whether the diagnostic system used (DSM *versus* ICD) or the level of development of the host country influenced the gender differences in age at onset (any of the four above definitions used) for schizophrenia. The Human Development Index (HDI; United Nations, 2001) was used to classify countries into developing (HDI 2 and 3 categories) and developed (HDI 1 category) countries.

Results

Assessment of publication bias

The funnel plot shown in Fig. A1 (see Appendix) is based on all studies reporting results for schizophrenia, regardless of the definition of age of onset. It is symmetrical about the line of estimated effect, demonstrating that publication bias is unlikely to be present.

Meta-analyses

I. Analyses for different definitions of age at onset

Age at first symptom in schizophrenia. A total of 17 estimates from 16 separate studies were included in this meta-analysis with a total sample size of 2609 males and 2016 females. Fig. 1 shows the forest plot with weighted effect size and 95% CI for each study. The weighted mean difference (WMD) in age of onset was −1.63 (95% CI −2.76 to −0.49), meaning that males had an earlier age at onset of 1.63 years.

Age at first positive symptom in schizophrenia. This meta-analysis included nine estimates from eight separate studies. The total sample consisted of 786 males and 573 females. Fig. 2 gives the forest plot with details of this meta-analysis. Males had an earlier onset by 1.43 years, with a WMD of −1.43 (95% CI −2.61 to −0.25).

Age at first consultation in schizophrenia. Fig. 3 gives the forest plot with weighted effect sizes and 95% CI for each individual study included in this meta-analysis. A total of 13 estimates from 12 studies were included in this meta-analysis examining the gender difference in age at first consultation in schizophrenia. The total sample size consisted of 1633 males and 1126 females. The overall WMD was −1.22, suggesting an earlier onset in males by 1.22 years. However, the 95% CI included zero (−2.49 to 0.06).

Age at first admission in schizophrenia. In this meta-analysis, 23 different estimates from 16 studies were included. The total sample size consisted of 17946 males and 11743 females. Fig. 4 shows the forest plot for this meta-analysis. The WMD was −1.07 (95% CI −1.93 to −0.21), indicating an earlier onset in males by 1.07 years.

II. Analysis for any definition for age at onset in schizophrenia

As the above meta-analysis showed an earlier age at onset in males compared with females, all the studies

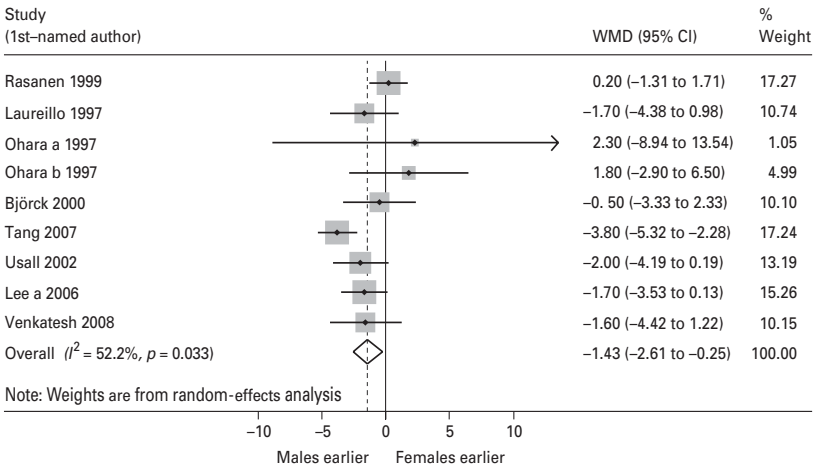

Fig. 2. Forest plot for gender difference in age (years) at first positive symptom of schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.

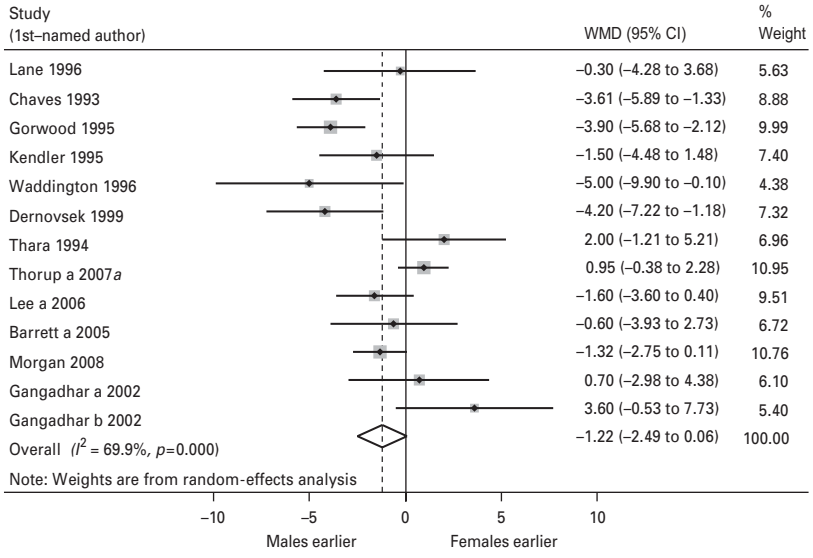

Fig. 3. Forest plot for gender difference in age (years) at first consultation for schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.

from the above four meta-analysis were combined in a separate meta-analysis. For each study, age at first symptom was used where reported. Otherwise, age at first positive symptom was used. If neither was reported, age at first consultation was used, and if none of the above was reported, then age of first admission was used. Fig. 5 gives the forest plot for the gender difference in age at onset of schizophrenia with any of the above four definitions for age at onset considered. A total of 30 estimates from 22 studies were included. The sample size consisted of 25684 males and 16802 females. This showed an earlier onset in males, with a WMD of −1.49 years (95% CI −2.07 to −0.92).

III. Age at first admission in non-affective psychoses

All the above meta-analyses examined gender difference in age at onset in schizophrenia. A further meta-analysis was conducted to examine the gender difference in age at onset in studies which included a broader group of disorders including schizo-affective disorders and all other non-affective psychoses. We used first admission, as this was the most frequently reported definition of onset. Fig. A2 (see Appendix) gives the forest plot for the results of this meta-analysis. A total of 30 estimates from 22 studies were included. The sample size consisted of 25684 males and 16802 females. The overall effect size was

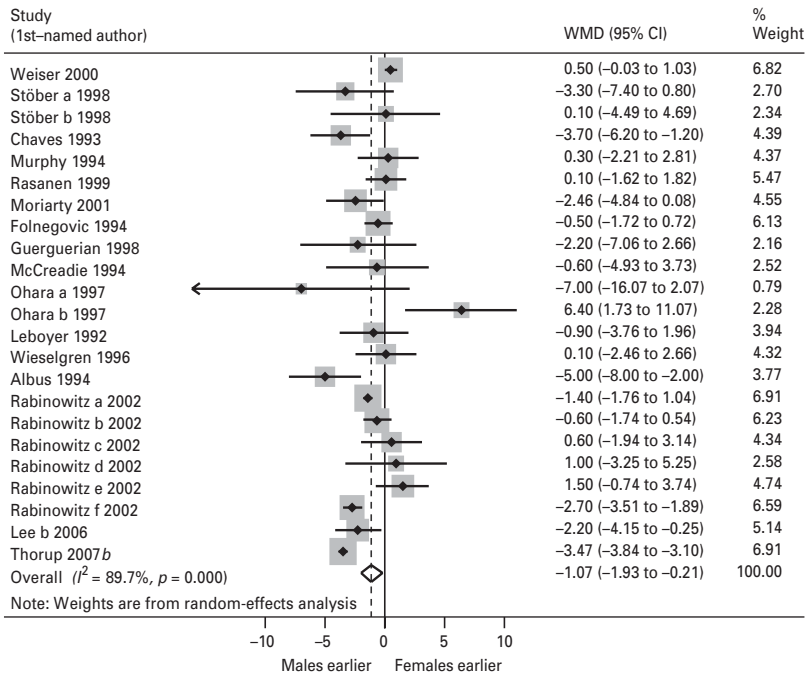

Fig. 4. Forest plot for gender difference in age (years) at first admission for schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.

−1.37 (95% CI −2.03 to −0.71), indicating an earlier first admission in males by 1.37 years in non-affective psychoses.

Meta-regression

Meta-regression analyses were conducted to examine the effect of two variables – diagnostic system used and developed/developing country status. Meta-regression was based on the meta-analysis of studies including any definition for age at onset of schizophrenia (see Fig. 5), adjusting for definition of age at onset in the analysis.

Diagnostic system used

A total of 48 estimates from 40 studies were included in this analysis. For ICD studies alone, the gender difference was non-significant, at −0.309 (95% CI −1.229 to 0.611, $p=0.510$), while for DSM studies it was −1.92 (95% CI −2.483 to −1.356, $p<0.001$). The meta-regression showed that the gender difference in age of onset was significantly greater under DSM criteria than ICD, adjusted for definition of age of onset (WMD = −1.93, 95% CI −3.11 to −0.75, $p=0.001$).

Developed versus developing country

The host countries of the studies were categorized according to the HDI into developed or developing countries. A total of 49 estimates from 40 studies were included in this analysis. The results showed no evidence of any difference in gender difference in age of onset between developing and developed countries (WMD adjusted for definition of onset = 1.68, 95% CI −1.41 to 1.75, $p=0.835$). The gender difference in developing countries was −1.54 (95% CI −2.85 to −0.23, $p=0.021$), and in developed countries was −1.43 (95% CI −2.11 to −0.77, $p<0.001$).

Discussion

Our results confirm a gender difference in the age at onset of schizophrenia, with an earlier age at onset in males. When all definitions for age at onset in schizophrenia are combined, males have an earlier onset by 1.49 years. The gender difference in age at onset is larger for age at onset of first symptom or positive symptom as compared with age at first consultation or admission (1.07 years). It is known that many patients have psychotic symptoms for some years before accessing services, and it is possible that the duration of time from the first symptoms to the first access to services is related to the patients' gender (Salokangas *et al*. 2003). We found the greatest gender difference (1.63 years) when 'age at first symptom' was used to define the age at onset of schizophrenia, and the smallest gender difference for age at first consultation (1.22 years) and age at first admission (1.07 years). This suggests that males may have a more insidious onset

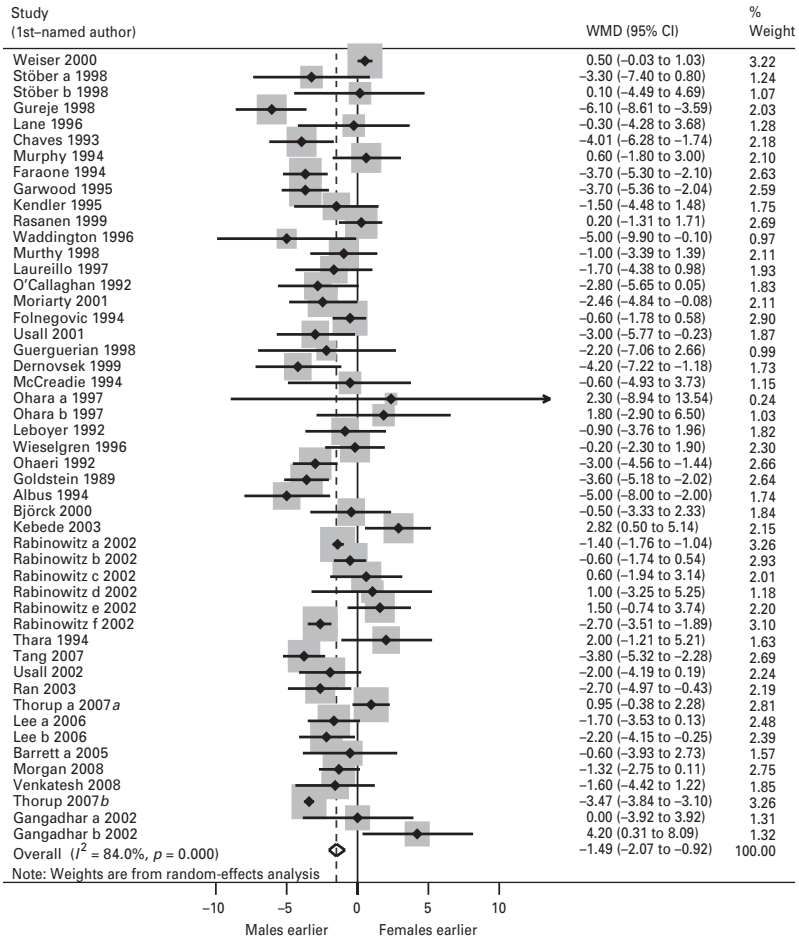

Fig. 5. Forest plot for gender difference in age (years) at onset (any definition) of schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.

of psychosis, with longer duration of untreated psychosis, than females.

There are some potential biases to consider. First, the majority of the studies are based on hospital patients or use registers that record hospital admissions. These hospitalized cases may be more severe or disturbed, and males may be overrepresented (Thorup *et al*. 2007*b*). Second, although we only included studies in working-age adults, there were some variations in lower and upper age limits of the studies, which may have influenced the size of the gender differences; for example, a study with an older upper limit may have included an excess of late-onset females.

The ascertainment of age at onset may not always have been accurate. For example, one study from South India (Murthy *et al*. 1998) describes the difficulties in ascertaining the age at onset in their sample in Bangalore, India. In patients who did not have date of birth records, assessment was made with information from family members using circumstantial evidence such as festivals or important national events. This highlights the difficulty in ascertaining age or age at onset in certain populations.

While we attempted to subdivide the studies according to the definition of onset used, this was not always straightforward. For example, one study defined age of onset as 'age at first symptom' but later stated that this was 'the age at which symptoms such as delusions, hallucinations, excitable or aggressive behaviour, catatonia, etc began'. The definition from this study was entered as 'age at first positive symptom'.

Furthermore, the point at which one begins to consider the presence of positive symptoms may be somewhat subjective, especially if clear cut hallucinations or delusions are not present. The demarcation of prodrome from onset of psychosis is also subjective, and may vary widely between clinicians. Gender differences in the ability to conceal symptoms may lead to earlier diagnosis in one gender than the other.

It has been demonstrated in previous studies that women have a second peak in incidence of

schizophrenia in later life, albeit much smaller than the peak in the early twenties (Thorup *et al*. 2007*a*). The estimate 'mean age at onset' does not take this into account and may produce skewed mean age at onset to the right for females. There is a suggestion that earlier-onset schizophrenia may be a different variant to later-onset cases (Kleinhaus *et al*. 2011). There is a need for further studies to examine gender differences in different age brackets.

In this meta-analysis, the gender difference is larger when a broader group of non-affective psychoses is included, with males being admitted 1.37 years earlier than females, compared with 1.07 years in schizophrenia. This broad group of psychoses included schizophrenia, schizo-affective disorders and other non-affective psychoses. The larger gender difference in age at onset in this group may be related to the inclusion of schizo-affective disorders. Studies of bipolar disorder have found a significant earlier onset in men, both for first depression and first mania (Viguera *et al*. 2001). A study of bipolar I disorder, in the suburbs of London, found that men had an earlier onset by 8.3 years (Viguera *et al*. 2001; Raymont *et al*. 2003), whilst a first-onset study in inner London over 35 years (Kennedy *et al*. 2005) showed that men had an earlier mean onset of bipolar disorder and mania by 4.4 and 5.1 years, respectively.

The results of the meta-regression for diagnostic criteria demonstrate that the diagnostic criteria used have a large impact on the gender difference in age of onset. Indeed, studies using ICD failed to show any gender difference in age of onset. Unlike ICD, DSM-III, DSM-III-R and DSM-IV require the existence of symptoms for a 6-month period for the diagnosis of schizophrenia. Our results imply that cases of a longer duration may show a greater gender difference in age of onset. Castle and colleagues showed that the application of criteria which define a severe form of schizophrenia (DSM criteria as compared with ICD criteria) excludes more females, and results in an overall male excess, especially in those with age at onset less than 25 years (Castle *et al*. 1998).

The results of the meta-regression demonstrate that the development index of the country has no effect on the gender difference in age at onset of core schizophrenia. This finding demonstrates the value of meta-analysis in addressing epidemiological questions. Many of the studies from developing countries that were included in the meta-analysis showed an earlier age of onset for males, but the fact that this difference was not significant in individual studies was sometimes interpreted by the authors as evidence for absence of gender difference, and as a result a narrative has developed in the literature suggesting that the gender difference may be absent in developing countries. In fact, the main difference between the developed and developing studies in this meta-analysis was that the latter were more heterogeneous: the estimate of between-study variance, τ^2, was 2.46 in the developed countries, but 4.63 in developing countries.

Three studies from developing countries included in the meta-regression found an earlier age at onset in females than males (Thara *et al*. 1994; Gangadhar *et al*. 2002; Kebede *et al*. 2003). However, the remaining seven studies from developing countries showed the expected earlier age at onset in males. The studies from developing countries had relatively small sample sizes. There is a need for larger studies from developing countries examining the gender difference in age at onset.

Limitations

Two databases, Ovid Medline and Web of Science, were used for literature searches. Personal communication from authors was sought for any clarification of data required. However, unpublished data or articles published in languages other than English were not included. This study did not examine gender differences in childhood-onset or late-onset schizophrenia. We were also not able to study the role of important confounders such as family history of schizophrenia, pre-morbid personality and obstetric complications as insufficient data were available. Lastly, our search covered only peer-reviewed journals. Although we cross-checked citations from individual papers, we may have missed some papers published in languages other than English and/or in non-peer-reviewed journals.

Conclusions

This meta-analysis shows a gender difference in age at onset of schizophrenia, with a small earlier age at onset in males. This difference is not specific to schizophrenia but is present in all non-affective psychosis. The gender difference was absent in studies using ICD-10 criteria but appeared confined to studies using DSM criteria, and was present to the same extent in studies from developed and developing countries. There is a need for large studies from developing countries to examine the gender difference in age at onset and factors influencing it. Further studies are required to examine the influence of confounding factors, such as family history of schizophrenia, pre-morbid personality and obstetric complications on gender differences in age at onset of schizophrenia.

Acknowledgements

This study was partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at King's College London and South London and Maudsley NHS Foundation Trust.

Declaration of Interest

None.

References

Albus M, Scherer J, Hueber S, Lechleuthner T, Kraus G, Zausinger S, Burkes S (1994). The impact of familial loading on gender differences in age at onset of schizophrenia. *Acta Psychiatrica Scandinavica* **89**, 132–134.

Angermeyer MC, Kuhn L (1988). Gender differences in age at onset of schizophrenia. An overview. *European Archives of Psychiatry and Neurological Sciences* **237**, 351–364.

Barrett R, Loa P, Jerah E, Nancarrow D, Chant D, Mowry B (2005). Rates of treated schizophrenia and its clinical and cultural features in the population isolate of the Iban of Sarawak: a tri-diagnostic approach. *Psychological Medicine* **35**, 281–293.

Bradburn MJ, Deeks JJ, Altman DG (1998). sbe24: metan – an alternative meta-analysis command. *Stata Technical Bulletin* **44**, 4–15.

Castle D, Sham P, Murray R (1998). Differences in distribution of ages of onset in males and females with schizophrenia. *Schizophrenia Research* **33**, 179–183.

Chaves AC, Seeman MV, Mari JJ, Maluf A (1993). Schizophrenia: impact of positive symptoms on gender social role. *Schizophrenia Research* **11**, 41–45.

Cohen RZ, Gotowiec A, Seeman MV (2000). Duration of pretreatment phases in schizophrenia: women and men. *Canadian Journal of Psychiatry – Revue Canadienne de Psychiatrie* **45**, 544–547.

Cohen RZ, Seeman MV, Gotowiec A, Kopala L (1999). Earlier puberty as a predictor of later onset of schizophrenia in women. *American Journal of Psychiatry* **156**, 1059–1064.

Dernovsek MZ, Tavcar R (1999). Age at onset of schizophrenia and neuroleptic dosage. *Social Psychiatry and Psychiatric Epidemiology* **34**, 622–626.

Everitt B (2003). Bayesian methods and meta-analysis. In *Modern Medical Statistics – A Practical Guide* (ed. B. Everitt), pp. 133–153. Oxford University Press Inc.: London.

Faraone SV, Chen WJ, Goldstein JM, Tsuang MT (1994). Gender differences in age at onset of schizophrenia. *British Journal of Psychiatry* **164**, 625–629.

Folnegovic-Smalc V, Folnegovic Z, Kulcar Z (1994). Age of disease onset in Croatia's hospitalized schizophrenics. *British Journal of Psychiatry* **156**, 368–372.

Gangadhar BN, Panner Selvan C, Subbakrishna DK, Janakiramaiah N (2002). Age-at-onset and schizophrenia: reversed gender effect. *Acta Psychiatrica Scandinavica* **105**, 317–319.

Goldstein JM, Faraone SV, Chen WJ, Tsuang MT (1989). Gender and the familial risk for schizophrenia. Disentangling confounding factors. *Schizophrenia Research* **7**, 135–140.

Gorwood P, Leboyer M, Jay M, Payan C, Feingold J (1995). Gender and age at onset in schizophrenia: impact of family history. *American Journal of Psychiatry* **152**, 208–212.

Guerguerian R, Lewine RR (1998). Brain torque and sex differences in schizophrenia. *Schizophrenia Research* **30**, 175–181.

Gureje O, Bamidele RW (1998). Gender and schizophrenia: association of age at onset with antecedent, clinical and outcome features. *Australian and New Zealand Journal of Psychiatry* **32**, 415–423.

Harbord RM, Higgins JPT (2008). Meta-regression in STATA. *Stata Journal* **8**, 293–519.

Kebede D, Alem A, Shibre T, Negash A, Fekadu A, Fekadu D, Deyassa N, Jacobsson L, Kullgren G (2003). Onset and clinical course of schizophrenia in Butajira-Ethiopia – a community-based study. *Social Psychiatry and Psychiatric Epidemiology* **38**, 625–631.

Kendler KS, Walsh D (1995). Gender and schizophrenia. Results of an epidemiologically-based family study. *British Journal of Psychiatry* **167**, 184–192.

Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, van Os J, Murray RM, Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, van Os J, Murray RM (2005). Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *American Journal of Psychiatry* **162**, 257–262.

Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Archives of General Psychiatry* **63**, 250–258.

Kleinhaus K, Harlap S, Perrin M, Manor O, Weiser M, Lichtenberg P, Malaspina D (2011). Age, sex and first treatment of schizophrenia in a population cohort. *Journal of Psychiatric Research* **45**, 136–141.

Lane A, Colgan K, Moynihan F, Burke T, Waddington JL, Larkin C, O'Callaghan E (1996). Schizophrenia and neurological soft signs: gender differences in clinical correlates and antecedent factors. *Psychiatry Research* **64**, 105–114.

Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L (1996). First-episode schizophrenia: II. Premorbid patterns by gender. *Schizophrenia Bulletin* **22**, 257–269.

Lauriello J, Hoff A, Wieneke MH, Blankfeld H, Faustman WO, Rosenbloom M, DeMent S, Sullivan EV, Lim KO, Pfefferbaum A (1997). Similar extent of brain dysmorphology in severely ill women and men with schizophrenia. *American Journal of Psychiatry* **154**, 819–825.

Leboyer M, Filteau MJ, Jay M, Campion D, Rochet T, D'Amato T, Feingold J, Des Lauriers A, Widlocher D (1992). No gender effect on age at onset in familial schizophrenia? *American Journal of Psychiatry* **149**, 1409.

Lee KY, Ahn YM, Joo E-J, Joo YH, Chang JS, Yoo HY, Kim YS (2006). Partial evidence of an association between epidermal growth factor A61G polymorphism and age at

onset in male schizophrenia. *Neuroscience Research* **56**, 356–362.

Lewine R, Haden C, Caudle J, Shurett R (1997). Sex-onset effects on neuropsychological function in schizophrenia. *Schizophrenia Bulletin* **23**, 51–61.

McCreadie RG, Connolly MA, Williamson DJ, Athawes RW, Tilak-Singh D (1994). The Nithsdale Schizophrenia Surveys. XII. 'Neurodevelopmental' schizophrenia: a search for clinical correlates and putative aetiological factors. *British Journal of Psychiatry* **165**, 340–346.

Morgan VA, Castle DJ, Jablensky AV (2008). Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Australian and New Zealand Journal of Psychiatry* **42**, 74–82.

Moriarty PJ, Lieber D, Bennett A, White L, Parrella M, Harvey PD, Davis KL (2001). Gender differences in poor outcome patients with lifelong schizophrenia. *Schizophrenia Bulletin* **27**, 103–113.

Murphy BM, Burke JG, Bray JC, Walsh D, Kendler KS (1994). An analysis of the clinical features of familial schizophrenia. *Acta Psychiatrica Scandinavica* **89**, 421–427.

Murthy GV, Janakiramaiah N, Gangadhar BN, Subbakrishna DK (1998). Sex difference in age at onset of schizophrenia: discrepant findings from India. *Acta Psychiatrica Scandinavica* **97**, 321–325.

O'Callaghan E, Gibson T, Colohan HA, Buckley P, Walshe DG, Larkin C, Waddington JL (1992). Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness: a controlled study. *BMJ* **305**, 1256–1259.

Ohaeri JU (1992). Age at onset in a cohort of schizophrenics in Nigeria. *Acta Psychiatrica Scandinavica* **86**, 332–334.

Ohara K, Xu HD, Mori N, Suzuki Y, Xu DS, Wang ZC (1997). Anticipation and imprinting in schizophrenia. *Biological Psychiatry* **42**, 760–766.

Pulver AE, Brown CH, Wolyniec P, McGrath J, Tam D, Adler L, Carpenter WT, Childs B (1990). Schizophrenia: age at onset, gender and familial risk. *Acta Psychiatrica Scandinavica* **82**, 344–3451.

Rabinowitz J, Fennig S (2002). Differences in age of first hospitalization for schizophrenia among immigrants and nonimmigrants in a national case registry. *Schizophrenia Bulletin* **28**, 491–499.

Rabinowitz J, Levine SZ, Hafner H (2006). A population based elaboration of the role of age of onset on the course of schizophrenia. *Schizophrenia Research* **88**, 96–101.

Ran M-S, Xiang M-Z, Li S-X, Shan Y-H, Huang M-S, Li S-G, Liu Z-R, Chen EY-H, Chan CL-W (2003). Prevalence and course of schizophrenia in a Chinese rural area. *Australian and New Zealand Journal of Psychiatry* **37**, 452–457.

Rasanen S, Veijola J, Hakko H, Joukamaa M, Isohanni M (1999). Gender differences in incidence and age at onset of DSM-III-R schizophrenia. Preliminary results of the Northern Finland 1966 birth cohort study. *Schizophrenia Research* **37**, 197–198.

Raymont V, Bettany D, Frangou S (2003). The Maudsley bipolar disorder project. Clinical characteristics of bipolar disorder I in a catchment area treatment sample. *European Psychiatry: Journal of the Association of European Psychiatrists* **18**, 13–17.

Salokangas RKR, Honkonen T, Saarinen S (2003). Women have later onset than men in schizophrenia – but only in its paranoid form. Results of the DSP project. *European Psychiatry: Journal of the Association of European Psychiatrists* **18**, 274–281.

Stöber G, Franzek E, Haubitz I, Pfuhlmann B, Beckmann H (1998). Gender differences and age of onset in the catatonic subtypes of schizophrenia. *Psychopathology* **31**, 307–312.

Subbakrishna DK, Murali N, Gangadhar BN, Janakiramaiah N (2001). Younger age at onset of schizophrenia in females: a replicative study. In *Statistical Methods and Application in Biology and Medicine* (ed. D. K. K. Subbakrishna and V. G. Kaliaperumal), pp. 253–260. NIMHANS: Bangalore, India.

Tang Y-L, Gillespie CF, Epstein MP, Mao P-X, Jiang F, Chen Q, Cai Z-J, Mitchell PB (2007). Gender differences in 542 Chinese inpatients with schizophrenia. *Schizophrenia Research* **97**, 88–96.

Thara R, Henrietta M, Joseph A, Rajkumar S, Eaton WW (1994). Ten-year course of schizophrenia – the Madras longitudinal study. *Acta Psychiatrica Scandinavica* **90**, 329–336.

Thorup A, Petersen L, Jeppesen P, Ohlenschlaeger J, Christensen T, Krarup G, Jorgensen P, Nordentoft M (2007*a*). Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. *Journal of Nervous and Mental Disease* **195**, 396–405.

Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M (2007*b*). Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychological Medicine* **37**, 479–484.

United Nations (2001). *Human Development Report*. United Nations: New York.

Usall J, Araya S, Ochoa S, Busquets E, Gost A, Marquez M; Assessment Research Group in Schizophrenia (2001). Gender differences in a sample of schizophrenic outpatients. *Comprehensive Psychiatry* **42**, 301–305.

Usall i Rodié J (2002). Sex and brain: morphological and functional differences between women and men (article in Spanish). *Actas Espanolas de Psiquiatria* **30**, 189–194.

Valigi Björck M, Själin M, Nordin C (2000). Neurological soft signs in schizophrenic patients: influence of age, age at onset, sex, and family history of schizophrenia. *Nordic Journal of Psychiatry* **54**, 437–440.

Venkatesh BK, Thirthalli J, Naveen MN, Kishorekumar KV, Arunachala U, Venkatasubramanian G, Subbakrishna DK, Gangadhar BN (2008). Sex difference in age of onset of schizophrenia: findings from a community-based study in India. *World Psychiatry* **7**, 173–176.

Viguera AC, Baldessarini RJ, Tondo L (2001). Response to lithium maintenance treatment in bipolar disorders: comparison of women and men. *Bipolar Disorders* **3**, 245–252.

Waddington JL, Youssef HA (1996). Familial-genetic and reproductive epidemiology of schizophrenia in rural

Ireland: age at onset, familial morbid risk and parental fertility. *Acta Psychiatrica Scandinavica* **93**, 62–68.

Weiser M, Reichenberg A, Rabinowitz J, Kaplan Z, Mark M, Nahon D, Davidson M (2000). Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. *Schizophrenia Research* **45**, 185–190.

Wieselgren IM, Lindstrom LH (1996). A prospective 1–5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. *Acta Psychiatrica Scandinavica* **93**, 9–19.

Appendix

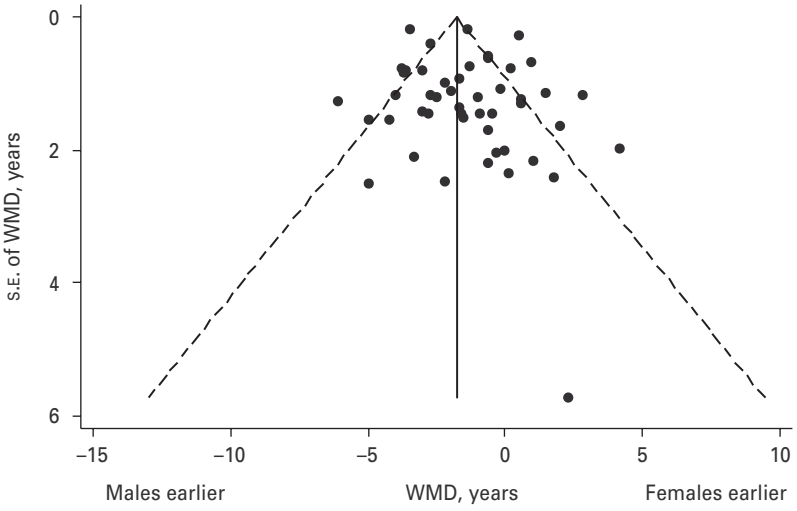

Fig. A1. Funnel plot with pseudo 95% confidence limits for studies using any definition of age of onset of schizophrenia (studies included in Fig. 5). S.E., Standard error; WMD, weighted mean difference.

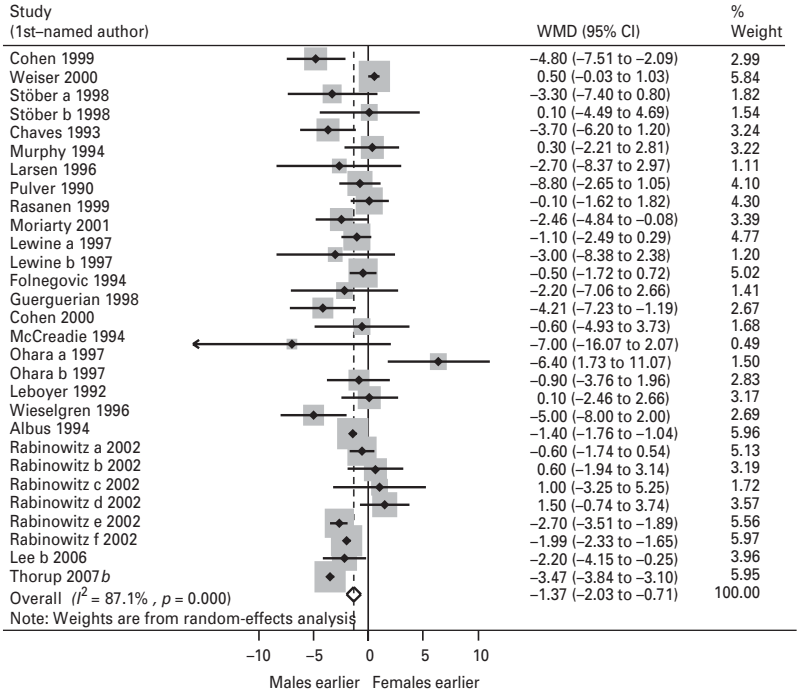

Fig. A2. Forest plot for gender difference in age (years) at first admission for any non-affective psychoses. For full details of study names, see Table A1. WMD, Weighted mean difference; CI, confidence interval.

Table A1. *Data for all studies included in the meta-analysis*

		Males					Females							
Study and reference	Year	Subjects, *n*	Age at first symptom, years	Age at first positive symptom, years	Age at first consultation, years	Age at first admission, years	Subjects, *n*	Age at first symptom, years	Age at first positive symptom, years	Age at first consultation, years	Age at first admission, years	Diagnostic criteria	Breadth of psychoses[a]	Country[b]
Albus (Albus *et al*. 1994)	1994	106				25 (9)	91				30 (12)	DSM-III-R	Narrow	1
Barrett a (Barrett *et al*. 2005)	2005	119			30.6 (13.0)		90			31.2 (11.5)		ICD-10	Narrow	2
Barrett b (Barrett *et al*. 2005)	2005	100			34 (14.3)		91			31 (13.9)		ICD-10	Broad	2
Björck (Valigi Björck *et al*. 2000)	2000	30		24.2 (5)			20		24.7 (5)			DSM-IV	Narrow	1
Chaves (Chaves *et al*. 1993)	1993	46	19.80 (4.12)		20.20 (4.19)	21.10 (4.90)	37	23.44 (5.86)		23.81 (6.01)	24.80 (6.40)	DSM-III-R	Narrow	2
Cohen (Cohen *et al*. 1999)	1999	45	18.6 (5.9)	22.4 (5.1)		24.2 (5.0)	35	19.9 (5.9)	26.7 (6.8)		29 (6.9)	DSM-IV	Broad	1
Cohen (Cohen *et al*. 2000)	2000	34	22.39 (4.91)			24.56 (4.75)	27	26.88 (6.58)			28.77 (6.80)	DSM-IV	Broad	1
Dernovsek (Dernovsek & Tavcar, 1999)	1999	100			27.8 (10.7)		100			32 (11.1)		ICD-10	Narrow	1
Faraone (Faraone *et al*. 1994)	1994	162	24.3 (6.1)				157	28 (8.3)				DSM-III	Narrow	1
Folnegovic (Folnegovic-Smalc *et al*. 1994)	1994	354	24.9 (7.8)			28.7 (8.2)	321	25.5 (7.8)			29.2 (8.0)	ICD-9	Narrow	2
Gangadhar a (Gangadhar *et al*. 2002)	2002	37	23.5 (8.5)		25.1 (7.9)		33	23.5 (8.2)		24.4 (7.8)		ICD-10	Narrow	2
Gangadhar b (Gangadhar *et al*. 2002)	2002	38	27.4 (8.6)		29.5 (8.5)		32	23.2 (8.0)		25.9 (9.0)		ICD-10	Narrow	2
Goldstein (Goldstein *et al*. 1989)	1989	171	24.3 (6.2)			25.5	161	27.9 (8.3)			28.9	DSM-III	Narrow	1
Gorwood (Gorwood *et al*. 1995)	1995	356	27.8 (9.7)		28.7 (10.1)		307	31.5 (11.8)		32.6 (12.9)		DSM-III-R	Narrow	2
Guerguerian (Guerguerian & Lewine, 1998)	1998	10				20.0 (3.1)	10				22.2 (7.2)	DSM-III-R	Narrow	1
Gureje (Gureje & Bamidele, 1998)	1998	56	23.1 (5.81)				64	29.2 (8.13)				DSM-III-R	Narrow	2
Kebede (Kebede *et al*. 2003)	2003	267	23.82 (8.6)				54	21.00 (7.8)				ICD-10	Narrow	2
Kendler (Kendler & Walsh, 1995)	1995	86			25.2 (6.8)		37			26.7 (8.1)		DSM-III-R	Narrow	1
Kirkbride (Kirkbride *et al*. 2006)	2006	333			29.6 (10.22)		235			32.6 (10.88)		DSM-IV	Broad	1
Lane (Lane *et al*. 1996)	1996	32	22.9 (5.8)				16	23.2 (7.0)				DSM-III-R	Narrow	1
Larsen (Larsen *et al*. 1996)	1996	28	24.5 (6.9)			27.5 (7.4)	15	29.7 (10.0)			30.2 (9.8)	DSM-III-R	Broad	1
Laureillo (Laureillo *et al*. 1997)	1997	18		16.6 (3.3)			19		18.3 (4.9)			DSM-III-R	Narrow	1
Leboyer (Leboyer *et al*. 1992)	1992	70				24 (6.5)	34				24.9 (7.2)	DSM-III-R	Narrow	1
Lee a (Lee *et al*. 2006)	2006	126		21.1 (5.4)	22.8 (5.9)		64		22.8 (6.4)	24.4 (7.0)		DSM-IV	Narrow	1
Lee b (Lee *et al*. 2006)	2006	116				23.1 (5.5)	63				25.3 (6.8)	DSM-IV	Narrow	1
Lewine a (Lewine *et al*. 1997)	1997	101				19 (3.4)	39				20.1 (3.9)	DSM-III-R	Broad	1
Lewine b (Lewine *et al*. 1997)	1997	29				32 (6.2)	22				35 (11.7)	DSM-III-R	Broad	1
McCreadie (McCreadie *et al*. 1994)	1994	31				23.8 (5.9)	15				24.4 (7.5)	ICD-9	Narrow	1

Table 1 (*cont.*)

Study and reference	Year	Males					Females					Diagnostic criteria	Breadth of psychoses[a]	Country[b]
		Subjects, *n*	Age at first symptom, years	Age at first positive symptom, years	Age at first consultation, years	Age at first admission, years	Subjects, *n*	Age at first symptom, years	Age at first positive symptom, years	Age at first consultation, years	Age at first admission, years			
Morgan (Morgan *et al*. 2008)	2008	394			23.34 (7.57)		199			24.66 (8.74)		ICD-10	Narrow	1
Moriarty (Moriarty *et al*. 2001)	2001	89				24.77 (8.54)	116				27.23 (8.72)	DSM-III-R	Narrow	1
Murphy (Murphy *et al*. 1994)	1994	109	24.9 (6.6)			26.1 (6.9)	57	24.3 (7.9)			25.8 (8.3)	DSM-III-R	Narrow	1
Murthy (Murthy *et al*. 1998)	1998	100	27.5 (8.0)				100	28.5 (9.2)		30.3 (9.7)		DSM-IV	Narrow	2
O'Callaghan (O'Callaghan *et al*. 1992)	1992	35	21.4 (5.1)				30	24.2 (6.4)				ICD-9	Narrow	1
Ohaeri (Ohaeri, 1992)	1992	199	24 (6)				141	27 (8)				DSM-IV	Narrow	2
Ohara a (Ohara *et al*. 1997)	1997	9		36.8 (15.90)		33.0 (13.10)	15		34.5 (8.50)		40.0 (5.94)	DSM-IV	Narrow	1
Ohara b (Ohara *et al*. 1997)	1997	18		21.9 (6.64)		24.4 (8.81)	7		20.1 (4.81)		18.0 (3.08)	DSM-IV	Narrow	1
Pulver (Pulver *et al*. 1990)	1990	258	20.9 (5.7)			23.7 (7.3)	93	21.2 (6.5)			24.5 (8.0)	DSM-III	Broad	1
Rabinowitz (Rabinowitz *et al*. 2006)	2006	7243				25.82 (8.19)	4828				27.81 (9.99)	ICD-9	Narrow	1
Rabinowitz a (Rabinowitz & Fennig, 2002)	2002	4434				23.9 (6.7)	3020				25.3 (8.5)	DSM-III-R	Narrow	1
Rabinowitz b (Rabinowitz & Fennig, 2002)	2002	576				24.1 (6.0)	193				24.7 (7.3)	DSM-III-R	Narrow	1
Rabinowitz c (Rabinowitz & Fennig, 2002)	2002	58				24.9 (4.8)	33				24.3 (6.5)	DSM-III-R	Narrow	1
Rabinowitz d (Rabinowitz & Fennig, 2002)	2002	14				25.5 (6.2)	19				24.5 (6.1)	DSM-III-R	Narrow	1
Rabinowitz e (Rabinowitz & Fennig, 2002)	2002	64				23.5 (6.1)	22				22 (4.0)	DSM-III-R	Narrow	1
Rabinowitz f (Rabinowitz & Fennig, 2002)	2002	1183				29.3 (9.1)	1059				32 (10.3)	DSM-III-R	Narrow	1
Ran (Ran *et al*. 2003)	2003	239	29.6 (13.5)				271	32.3 (12.5)				ICD-10	Narrow	2
Rasanen (Rasanen *et al*. 1999)	1999	58		21.4 (3.4)		21.5 (4.0)	31		21.2 (3.5)		21.4 (3.9)	DSM-III-R	Narrow	1
Stöber a (Stöber *et al*. 1998)	1998	42				23.2 (8.0)	41				26.5 (10.8)	DSM-III-R	Narrow	1
Stöber b (Stöber *et al*. 1998)	1998	42				20.8 (6.9)	14				20.7 (7.8)	DSM-III-R	Narrow	1
Tang (Tang *et al*. 2007)	2007	298		24.8 (8.1)			244		28.6 (9.6)			DSM-IV	Narrow	2
Thara (Thara *et al*. 1994)	1994	40			24 (6)		36			22 (8)		ICD-9	Narrow	2
Thorup (Thorup *et al*. 2007*b*)	2007	10341				29.31 (10.16)	6421				32.78 (12.82)	Mixed	Narrow	1
Thorup a (Thorup *et al*. 2007*a*)	2007	211	23.7 (6.19)		26.7 (6.42)		140	22.7 (5.99)		25.7 (6.06)		ICD-10	Narrow	1
Thorup b (Thorup *et al*. 2007*a*)	2007	274	24.30 (6.39)		26.65 (6.20)		183	24.25 (6.79)		26.40 (6.44)		ICD-10	Broad	1
Usall (Usall *et al*. 2001)	2001	143	23 (10)				77	26 (10)				DSM-IV	Narrow	1
Usall (Usall i Rodié, 2002)	2002	126		22 (5.8)			74		24 (8.5)			DSM-IV	Narrow	1

Venkatesh (Venkatesh *et al*. 2008)	2008	103		29.2 (8.8)			99		30.8 (11.4)			ICD-10	Narrow	2
Waddington (Waddington & Youssef, 1996)	1996	48			25.6 (7.1)		35			30.6 (13.5)		DSM-III-R	Narrow	1
Weiser (Weiser *et al*. 2000)	2000	90				20.1 (1.8)	90				19.6 (1.8)	ICD-9	Narrow	2
Wieselgren (Wieselgren & Lindstrom, 1996)	1996	86	22.4 (4.4)			27.1 (6.3)	34	22.6 (5.6)			27.0 (6.5)	DSM-III-R	Narrow	1

DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R, DSM Third Edition Revised; ICD, International Classification of Diseases; ICD-10, ICD Tenth Revision; DSM-IV, DSM Fourth Edition; DSM-III, DSM Third Edition; ICD-9, ICD Ninth Revision.

Age at onset given as mean (standard deviation).

[a] Breadth of psychosis: narrow = schizophrenia; broad = schizophrenia, schizo-affective disorders and all non-affective psychosis. [b] Country: 1 = developed country; 2 = developing country.